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COMMUNICATION

KOH-mediated transition metal-free synthesis of imines from alcohols and amines†

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The various imines were prepared from alcohols and amines in moderate to good yields under an air atmosphere promoted by KOH, eliminating the need for toxic transition metal catalysts. Due to its simplicity, this protocol will have wide application in synthesis.

Introduction

The development of environmentally benign, tandem and cross-coupling strategies is an important goal in contemporary organic synthesis because of economy and environmental impact. In recent years, a part of this drive is to avoid or minimize the use of noble metals in tandem cross-coupling reactions, as these are sometimes toxic, expensive and difficult to dispose off properly in large quantities.

Imines are frequently found as substructures in a diverse array of compounds, including a wide range of natural products, biologically and therapeutically active substances.[1] Imines are also of great importance as intermediates in the synthesis of various useful organic compounds.[2] Therefore making them efficiently is of paramount importance. The conventional methods for the synthesis of imines involve the condensation of a primary amine with a carbonyl.[3] In the past few years, great efforts have been made to develop environmentally friendly processes toward imine synthesis. The catalytic synthesis of imines from secondary amines[4] and oxidative condensations of primary amines[5] were also reported in the literature. Recently, transition metal-catalyzed oxidative imine synthesis directly from alcohols and amines, without any oxidative preparation of aldehydes, has been highlighted as a highly atom economical transformation that generates water as the sole byproduct. Since the seminal work of Milstein,[6] a wide range of metal complexes have been used as catalysts in this coupling reaction including ruthenium,[7] osmium,[8] palladium,[9] platinum,[10] gold,[11] copper[12] *etc.*

To our knowledge, the direct condensation of primary amines with primary alcohols without any transition metal complex for the synthesis of imines was not yet known. We have previously observed a trace amount of β-alkylation of lactic acid with primary alcohols in the presence of KOH but without a transition metal catalyst,[13] in which the "KOH-promoted dehydrogenative oxidation of alcohols" was the most crucial step in the reaction pathway. On the basis of this concept, an 85% yield of benzoic acid was obtained when benzyl alcohol (3.0 mmol) and KOH (3.0 mmol) was heated in toluene at 110 °C for 40 h under aerobic conditions. It was suggested that this might provide an efficient approach for base-mediated reactions of amines with carbonyls that should rely on the dehydrogenation of alcohols.

Results and discussion

To test this hypothesis, benzyl alcohol (**1a**) and aniline (**2a**) were used as the substrates in these studies. When a mixture of **1a** (3.6 mmol) and **2a** (3.0 mmol) and KOH (6.0 mmol) was heated in toluene at 110 °C for 20 h under aerobic conditions. The reaction gave the desired product, *N*-benzylideneaniline (**3a**), in 92% yield (^{1}H NMR yield) (Table 1, entry 1). The structure of **3a** was confirmed by ^{1}H, ^{13}C, and ESI-MS analysis. After this initial promising result, we studied the effect of base and solvent on the reaction yield. Various bases were tested for the catalytic reaction. Among them, KOH gave the highest yield of product **3a**. NaOH also showed catalytic activity for the reaction, but provided coupling products in only 60% yield (Table 1, entry 4). Some strong bases, *t*-BuONa and *t*-BuOK (Table 1, entries 2–3), gave high conversions of the starting materials but the product in low yield. Others such as K_2CO_3 and triethylamine were less effective, giving **3a** in very low yield (Table 1, entries 5–7). Increase in the amount of KOH did not have any appreciable impact on the chemical yield (Table 1, entries 1, 8 and 9). In the presence of 0.2 equiv of CsOH, good solubility in toluene, 87% product was formed (Table 1, entry 15). Because reagent-grade KOH is known to have transition metal contaminants, semiconductor-grade KOH, 99.99% pure based on trace metal analysis (Alfa Aesar), was also examined (Table 1, entry 10). As seen in Table 1, the use of semiconductor-grade KOH did not change the product or yield *versus* the reagent-grade base. The screening of a range of solvents showed that the toluene was the best choice (Table 1, entries 1 and 14). Lowering the reaction temperature to 90 °C still gave 91% of **3a** under the same conditions (Table 1, entry 14). Under argon atmosphere, no desired product was observed (Table 1, entry 16).

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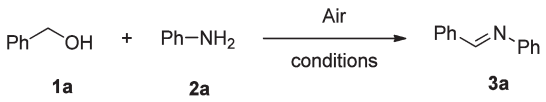
Table 1 Reaction conditions optimization[a]



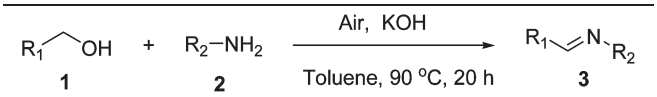
Entry	Base	Solvent	T (°C)	Yield[b] (%)
1	KOH	Toluene	110	92
2	*t*-BuONa	Toluene	110	56
3	*t*-BuOK	Toluene	110	18
4	NaOH	Toluene	110	60
5	K_2CO_3	Toluene	110	5
6	Cs_2CO_3	Toluene	110	3
7	Et_3N	Toluene	110	Trace
8[c]	KOH	Toluene	110	91
9[d]	KOH	Toluene	110	85
10[e]	KOH	Toluene	110	91
11	KOH	THF	66	56
12	KOH	Dioxene	101	80
13[d]	KOH	H_2O	100	0
14	KOH	Toluene	90	91
15[f]	CsOH	Toluene	90	87
16[g]	KOH	Toluene	90	Trace

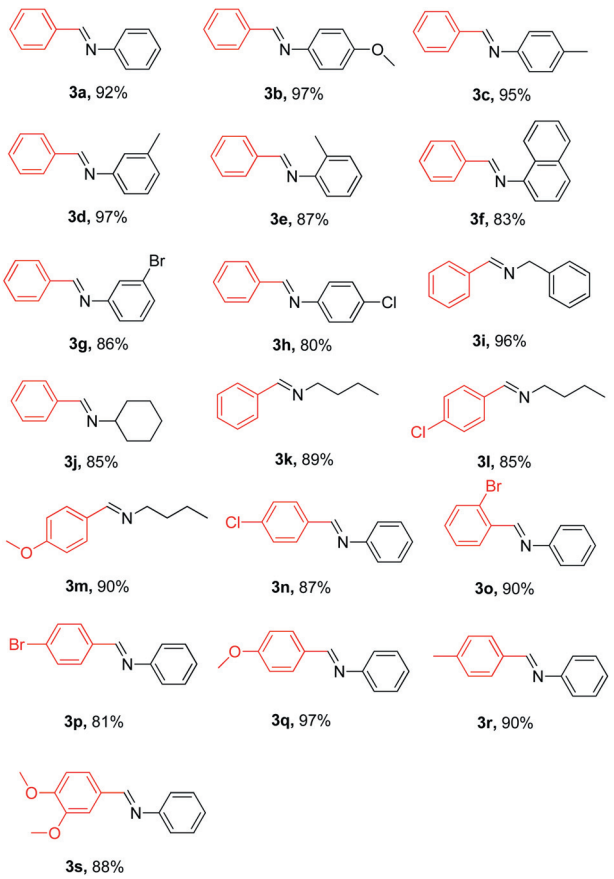
[a] Reaction conditions: benzyl alcohol (3.6 mmol) and aniline (3.0 mmol), base (6.0 mmol), 2.5 mL toluene (reflux), open to air, 20 h. [b] Yields were determined by ^{1}H NMR using an internal standard (anisole). [c] 3.6 mmol KOH was used. [d] 0.8 equiv. of KOH was used. [e] Denotes use of semiconductor-grade KOH. [f] 0.2 equiv. of CsOH was used. [g] In argon ambient.

With these optimized reaction conditions, a variety of substrates were surveyed to explore the scope and limitations of the reaction (Table 2). In all cases, the corresponding *N*-alkylation products were detected in 2–10% yields by ^{1}H NMR. Our KOH-mediated system is effective for a wide combination of primary amines and benzyl alcohols giving the corresponding imines in good yields under aerobic atmosphere. The reaction of aromatic amines with **1a** afforded **3a–h** in 80–97% yields. Similarly, the reaction of aliphatic amines with **1a** gave **3i–m** in 85–96% yields. The above results indicate that both aliphatic and aromatic amines work equally well with the reaction. Substituted benzyl alcohols with 4-methoxy and 4-chloro groups also reacted smoothly with aniline to afford products **3q** and **3n** in 97 and 87% yields. Similarly, treatment of benzyl alcohol with 4-methoxy and 4-chloro substituted anilines led to the formation of products **3b** and **3h** in 97 and 80% yields, respectively. The above results indicated that electron-withdrawing groups on the phenyl ring substrates would significantly lower the yield. In addition, this reaction was also compatible with bromo and chloro substituents on the aromatic ring of benzyl alcohol and aniline. Treatment of benzyl alcohol with 4-methyl and 2-methyl substituted anilines afforded **3c** and **3e** in 95 and 87% yields, respectively. Nevertheless, sterically bulkier 2,6-dimethyaniline reacted with **2a**, gave the corresponding imine in very low yield. 1-Phenylethanol and aliphatic primary alcohols were also examined. Unfortunately, no desired imine products were detected by ^{1}H NMR.

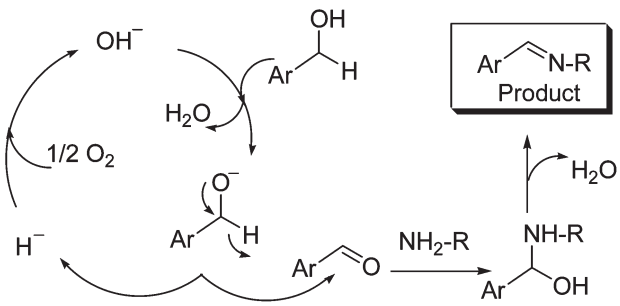
The detailed reaction mechanism remains to be clarified. Important recent studies have shown the use of alkali metal bases for the oxidation of alcohols to the corresponding carbonyls in excess acetone through an Oppenauer pathway.[14]

Table 2 Base-mediated aerobic oxidative imines preparation from alcohols and amines[a]





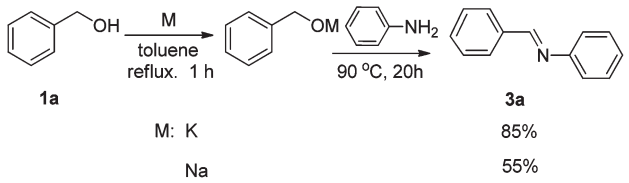
[a] Reaction conditions: benzyl alcohol (3.6 mmol) and aniline (3.0 mmol), KOH (3.6 mmol), 2.5 mL toluene, open to air, 90 °C, 20 h. Yields were determined by ^{1}H NMR using an internal standard (anisole).



Scheme 1 Plausible reaction mechanism.

Because no ketone is included[15] in our reaction mixtures, another pathway must be responsible for the product formation, as shown in Scheme 1.

The real role of the strong base is clear from a mechanistic point of view; it is connected initially with the deprotonation of



Scheme 2 Imines preparation from amines and alkali metal alkoxides. Reaction conditions: (1) benzyl alcohol (3.6 mmol) and metal (3.2 mmol), 5 mL toluene (reflux) in nitrogen atmosphere, 60 min, alkali metal alkoxide was prepared; (2) aniline (3.0 mmol), open to air, 90 °C, 20 h. Yields were determined by ^{1}H NMR using an internal standard (anisole).

the aryl-alcohol leading to the formation of the potassium aryl-carbinoate intermediate; this intermediate could extrude a H^-, the Cannizzaro-like reaction[16] under strong base or β-hydride elimination in metal-catalyzed reactions,[13,17] to form aryl-aldehyde. Benzaldehyde was also detected by ^{1}H NMR in the reaction solution. The same reaction using the *in situ*-prepared alkali metal alkoxides (by deprotonation of benzyl alcohol with potassium and sodium, Scheme 2) yield the expected product **3a** in good yields. This results also make the involvement of transition metal traces in the base-promoted synthesis of imines impossible.

Subsequently, the formed H^- could react with O_2 to form OH^-. When the reaction was performed using aniline and benzyl alcohol under nitrogen atmosphere, compound **3a** was not detected after 20 h, indicating that oxygen also has a significant role in the catalytic reaction (Table 1, entry 2). The cross coupling reaction of the amine with aldehyde generated affords the product imine.

Wang's group reported the aerobic oxidation of a secondary aryl-alcohol into its ketone promoted by NaH, and observed the formation of hydrogen peroxide (NaOOH) in the reaction system.[18] After the imine synthesis completed in the KOH-mediated reaction, the recovered insoluble powder was dissolved in water and made acidic with HCl, H_2O_2 was not detected by the potassium iodide/starch test. Moreover, only a 20% equivalent of CsOH can also promoted the imine synthesis (Table 1, entry 15) and aerobic oxidation of sec-aromatic alcohols.[19] The above results proved that not OOH^- but OH^- was formed in the KOH-mediated imine synthesis.

Conclusions

In summary, we have established the first example of a base-promoted green synthesis of highly desirable imines starting from amines and alcohols. Both the use of air as an environment-friendly oxidant and the elimination of transition metal catalyst all constitute the charming characters of this procedure, rendering the experimental procedure very simple. Therefore, this protocol will have wide application for the construction of natural products, biologically and therapeutically active compounds.

Experimental

All reactions were carried out under air. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were measured on Bruker 400M spectrometers with $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard. Chemical shifts were reported in units (ppm) by assigning TMS resonance in the ^{1}H spectrum as 0.00 ppm and $CDCl_3$ resonance in the ^{13}C spectrum as 77.0 ppm. All coupling constants (*J* values) were reported in Hertz (Hz). Chemical shifts of common trace ^{1}H NMR impurities (ppm): H_2O: 1.56, $CHCl_3$: 7.26. Column chromatography was performed on basic alumina gel 200–300 mesh using petroleum ether and ethyl acetate as the eluent. The CAS number of the known compound was listed.

General procedure for the synthesis of 3a

A mixture of 3.0 mmol of aniline (**1a**), 3.6 mmol of benzyl alcohol (**2a**), 3.6 mmol of potassium hydroxide in 2.5 mL toluene was stirred under an atmosphere of air at 90 °C for 24 h. The reaction mixture was then, without any workup, purified directly by column chromatography on basic alumina gel (petroleum ether (60–90 °C)–ethyl acetate–triethylamine 100 : 10 : 1) to afford imine (**3a**) in 83% isolated yield.

Acknowledgements

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